1-2. Applicants note with appreciation that Groups I-X are rejoined into Group I. Applicants acknowledge that claims 6-13, 16 and 21-23 are withdrawn from consideration as being directed to nonelected Groups XI-XVII. Claims 1-5, 14, 15 and 17-38 are currently under consideration.

3. Applicants' amendment to the specification is believed to satisfy the requirements for receiving benefit of an earlier filing date under 35 U.S.C. 120.

4-5. Applicants have amended the specification to comply with the requirements of 37 CFR 1.821 through 1.825. Applicants' amendments are believed to obviate the objection to the specification.

6. Claims 4, 14, 17, 18 and 20 are objected to due to certain informalities. Applicants' correction of these typographical errors is believed to obviate the objection.

7-8. Claims 1-5, 14, 15 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skill in the art that the inventor had possession of the claimed invention. Specifically, the office action alleges that there is no support in the originally filed claims or specification to support the recitation of "ligand-crosslinked complex", and that this language constitutes new matter. Applicants respectfully traverse this rejection.

Applicants contend that the amended subject matter which refers to a "ligand-crosslinked complex" is supported by the application, as filed. The application explicitly incorporates by references the publications, patents and patent application cited in the specification. "The full contents of all references cited in this document, including references from the scientific literature, issued patents and published patent applications, are hereby expressly incorporated by reference." (page 34, lines 8-10). More specifically, "design, production and use of DNA constructs and ligands for the practice of this invention may take advantage of principles, materials, and methods discussed in any of the following: PCT/US94/01667 and PCT/US94/08008 (Crabtree and Schreiber et al), PCT/US95/16982 (Pomerantz et al), PCT/US95/10559 and PCT/US97/03137 (Holt et al), PCT/US96/09948 (Clackson et al), PCT/US95/10591 (Brugge et al) and PCT/US97/22454 (Cerasoli), as well as US priority applications identified in any of the foregoing." (page 5, lines 3-8).

To more particularly demonstrate that the present application provides adequate support for the recitation of "ligand-crosslinked complex", applicants refer the Examiner to PCT/US94/08008. Specifically, Applicants contend that the following passages are indicative of the expressly and implicitly disclosed subject matter of the present application. "The realization that membrane receptors could be activated by homodimerization resulted from the observation that receptors could be activated by antibodies that cross linked two receptors." (page 1, lines 18-21). "Our invention, which is disclosed in detail hereinafter, involves a generally applicable method and materials for utilizing protein homodimerization, heterodimerization and oligomerization in living cells. (As used herein, the terms oligomer, oligomerize and oligomerization encompass dimers, trimers and higher order oligomers and their formation). Chimeric responder proteins are intracellularly expressed as fusion proteins with a specific receptor domain. Treatment of the cells with a cell permeable multivalent ligand reagent which binds to the receptor domain leads to dimerization or oligomerization of the chimera." (page 2, line 31-page 3, line 2). "Intracellular crosslinking of chimeric proteins by synthetic ligands has potential in basic investigation of a variety of cellular processes, in regulatably initiating cell death in engineered cells and in regulating the synthesis of proteins of therapeutic or agricultural importance. Furthermore, ligand mediated oligomerization now permits regulated gene therapy." (page 3, lines 9-13). "This invention provides chimeric proteins, organic molecules for oligomerizing the chimeric proteins and a system for using them. The fused (chimera) have a binding domain for binding to the (preferably small) organic oligomerizing molecule and an action domain, which can effectuate a physiological action or cellular process as a result of oligomerization of the chimeric proteins." (page 14, lines 26-31). Additional passages which support Applicants' contention that the pending claims satisfy all of the requirements under 35 U.S.C. 112, first paragraph, include, without limitation, page 5, lines 22-26; page 7, lines 21-29; and page 10, lines 1-28.

Applicants remind the Examiner that in accordance with MPEP 2163, amendments to the claims need not find in haec verba support in the specification. All that is required in that those claim limitation are "supported in the specification through express, implicit, or inherent disclosure." (MPEP 2163). Applicants maintain that this burden has been satisfied. One of skill in the art would recognize that the disclosure of PCT/US94/08008, as well as the disclosures of other patents and patent applications incorporated by reference into the present application in

their entirety, support the phrase "ligand-crosslinked complex". In accordance with MPEP 2163.07(b), "information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed." Accordingly, claims 1-5, 14, 15 and 17-20 satisfy all of the requirements under 35 U.S.C. 112, first paragraph.

Despite Applicants contention that the specification supports recitation of "ligand-crosslinked complex", Applicants have amended the claims to pursue additional embodiments of the invention supported by the specification. Applicants amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar of differing scope. Applicants' amendments render this rejection moot, and reconsideration and withdrawal of this rejection are respectfully requested.

9. Claims 14, 15, 18-20 and 24-38 are rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to enable one of skill in the art to use the invention commensurate in scope with the claims. Specifically, the office action alleges that while the specification is enabling for regulating expression of a target gene in vitro, it does not provide enablement for regulating expression of a target gene in vivo. Applicants respectfully traverse this rejection.

The basis of the Examiner's rejection is that Applicants have allegedly failed to demonstrate that this regulatable gene expression system can be used to modulate gene expression in vivo. Applicants contend that the Examiner's characterization of this technology is incorrect. Applicants direct the Examiner's attention to Ye et al., 1999 and Rivera et al., 1999 (enclosed herewith as Exhibits 1 and 2) which demonstrate that regulatable gene expression technology based on genetic constructs which can be oligomerized by a selected ligand (for example, the small molecule rapamycin) can be successfully used to modulate the expression of a therapeutic protein in vivo. Ye et al. demonstrated the successful rapamycin-dependent expression of erythropoietin in both mice and non-human primates. "There was no increase in plasma Epo or change in hematocrit before challenge with rapamycin for a period of either 30 or 71 days after vector administration. Single administration of rapamycin resulted in an immediate 100-fold rise in plasma Epo to 100 to 150 mU/ml that returned to baseline within 14 days. A more sustained increase in plasma Epo was achieved after repeated rapamycin administrations. Induction of Epo resulted in an increase in hematocrit to 70 to 75%, which slowly returned to

baseline over a 2- to 3-month period after the withdrawal of rapamycin, consistent with the half-life of erythrocytes in mice." (Ye et al., 1999, page 88, column 3).

Similarly, Rivera et al. reported successful, rapamycin regulated expression of human growth hormone expression in mice. "In the absence of rapamycin, basal plasma levels of hGH were below the detection limit of the assay. A single i.p. injection of rapamycin (5 mg/kg) resulted in at least a 100-fold increase in plasma hGH. hGH levels then diminished to baseline over the next 14 days. Similar induction profiles were noted after five subsequent injections of rapamycin administrated periodically over 6 months. The peak level of induced hGH was similar to that seen in animals injected with an equal quantity of an adenovirus expressing hGH from the strong constitutive enhancer/promoter of the immediate early gene of CMV; in each case the peak level diminished approximately 10-fold over the 6-month period." (Rivera et al., 1999, page 8658, column 2).

The disclosures of Ye et al. and Rivera et al., demonstrate that a regulatable gene expression system can be used successfully to deliver therapeutic proteins in vivo in a ligand dependent manner. These successful in vivo examples, in combination with the teachings of the present application which provide particular constructs and reagents which can be used to modulate angiogenesis in a ligand-dependent manner, support the enablement of the presently claimed subject matter. Accordingly, Applicants contend that the claims are enabled throughout their scope, and reconsideration and withdrawal of this rejection are respectfully requested.

10-13. Claims 1-5, 14, 15, 17-20 and 24-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

a. Claim 1 and claim 14 are rejected over the recitation of "ligand crosslinked protein complex". As outlined in detail above in response to the rejection of the term "ligand crosslinked protein complex", Applicants contend that the term is adequately described in the specification as filed. Applicants refer the Examiner to the passages of PCT/US94/08800 cited above to demonstrate the ample and complete description of the presently claimed subject matter. Accordingly one of skill in the art can readily envision the metes and bounds of the claimed subject matter.

Nevertheless, as outlined in detail above, Applicants have amended the claims to pursue additional embodiments supported by the specification. Applicants' amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Applicants' amendments render the rejection moot, and reconsideration and withdrawal of this rejection is respectfully requested.

14-15. Claims 1-5, 14, 15, 17-20 and 24-38 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by U.S. 5,654,168 (the '168 patent). Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

The '168 patent fails to satisfy the criteria for anticipating Applicants' invention. Both the MPEP and the Federal Circuit support Applicants' contention that in order to anticipate or render obvious the claimed invention, the cited art must teach all the limitations of the claimed subject matter (MPEP 2131). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegall Bros. v. Union Oil Company of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the .... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ3d 1913, 1920 (Fed. Cir. 1989). The '168 patent fails to teach the particular combination of elements of the pending claims.

Nor is the claimed subject matter obvious in view of the teachings of the '168 patent. Applicants contend that a valid patent may issue for a nonobvious species related to a prior patented invention. A prior genus which does not explicitly disclose a species does not anticipate a later claim to that species. This position is well supported by the holdings of the Federal Circuit. See, for example, *Corning Glass Works v. Sumitomo Electric U.S.A.*, 868 F.2d 1251, 1262, 9 USPQ2d 1962, 1970 (Fed. Cir. 1989).

Applicants contend that the relationship between the pending claims and the cited art is largely analogous to the factual situation in the above example. Applicants assert that the presently claimed invention is unobvious and patentable over the teachings of '168 patent.

Applicants contend that the '168 patent fails to teach or suggest all the limitations set forth in the claims. Although the '168 patent provides compositions and methods used for

regulating gene expression, the '168 patent fails to teach the benefits of the particular combinations of agents set forth in the pending claims. That is, the '168 patent provides no motivation to specifically select the particular elements presently claimed. MPEP 2144.08 outlines the guidelines for determining that a reference renders an invention obvious and directs the Examiner to "determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, i.e., to select the claimed species or subgenus from the disclosed prior art genus." Applicants contend that the '168 patent fails to provide motivation to select a particular angiogenesis inhibitor. Furthermore, the Examiner has not provided any evidence or additional references that would have motivated one of skill in the art to arrive at Applicants' invention.

Applicants maintain that the '168 patent fails to satisfy the criteria necessary for anticipating or rendering obvious Applicants' invention. Nevertheless, to expedite prosecution of claims directed to commercially relevant subject matter, Applicants have amended the claims to more particularly point out the features of the claimed invention. Applicants' amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection is requested.

16-17. Claims 1-5, 14, 15, 17-20 and 24-38 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over U.S. 5,654,168 in view of WO94/18317. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

Applicants have discussed in detail above why the '168 patent does not anticipate the claimed subject matter. WO94/18317 does not overcome the deficiencies of the '168 patent with regard to selecting a particular angiogenesis inhibitor, as recited in the pending claims. Given that WO94/18317 fails to overcome the deficiencies of the '168 patent, Applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

Date: February 13, 2003

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